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| 09/868,469      | 09/24/2001  | Stephen J. Benkovic  | 6460-18-1           | 1582             |

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EXAMINER

FRONDA, CHRISTIAN L

|          |              |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
|----------|--------------|

1652

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/868,469

**Applicant(s)**

BENKOVIC ET AL.

**Examiner**

Christian L. Fronda

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 05 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-127 is/are pending in the application.
- 4a) Of the above claim(s) 12, 13, 41-52 and 90-127 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-11, 14-40 and 53-89 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 September 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 06/15/2001.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

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## **DETAILED ACTION**

### ***Election/Restriction***

1. Applicants election with traverse of Group I, (claims 1-11, 14-40, and 53-89) filed 08/05/2004 has been acknowledged. Applicants' arguments for traversing the restriction filed 08/05/2004 that the cited reference of Holford et al. does not teach the technical feature of among the claims are not persuasive for the reasons of record as supplemented below.

The claims do not recite the limitation that the N-terminal intein is not the N-terminus of the peptide and the C-terminal intein is not the C-terminus thioester. Claims must be given broad interpretation to determine the scope of the invention. As stated in the previous Office Action, The specification defines the word "intein" is a polypeptide sequence that can catalyze a splicing reaction during post-translational processing of a protein (see p. 13, lines 3-5). Thus, when the teachings Holford et al. are read in view of this definition of "intein", the N-terminal polypeptide sequence of the recombinant protein containing the introduced N-terminal cysteine is deemed to be the first portion of a split intein; the C-terminal polypeptide sequence containing the introduced C-terminal thioester is deemed to be the second portion of a split intein; and the polypeptide sequence in between is deemed to be the target peptide that is to be cyclized. Thus, the technical feature is not special since it was known in the prior art and therefore cannot make a contribution over the prior art.

2. Claims 1-11, 14-40, and 53-89 are under consideration in this Office Action.

### ***Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-11, 14-40, and 53-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

The claims are vague and indefinite for recitation of the phrases "first portion" and

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“second portion”. The metes and bounds of the claim are uncertain since it is not clear if the term “portion” is to mean one amino acid or several amino acids.

The phrase “derived from” renders the claims vague and indefinite since it is unclear if the claimed split intein would have any amino acid sequence and structure that is common to RecA, DnaB, PspPol-I, Pfu, or SspDnaE inteins.

***Claim Rejections - 35 U.S.C. § 112, 1st Paragraph***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-11, 14-40, and 53-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the evaluation of the claims for compliance with the written description requirement of 35 U.S.C. 112, of particular relevance is 66 FR 1099, Friday, January 5, 2001, which states:

“*Eli Lilly* explains that a chemical compound’s name does not necessarily convey a written description of the named chemical compound, particularly when a genus of compounds is claimed. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1405. The name, if it does no more than distinguish the claimed genus from all others by function, does not satisfy the written description requirement because “it does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Thus *Eli Lilly* identified a set of circumstances in which the words of the claim did not, without more, adequately convey to others that applicants had possession of what they claimed.” (see p. 1100, 1<sup>st</sup> column, line 47 to 2<sup>nd</sup> column, line 2).

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The claims are genus claim that is directed toward a genus of inteins; a genus of split inteins; a genus of split inteins derived from RecA, DnaB, PspPol-I, or Pfu inteins; a genus of split inteins derived from SspDnaE.

The scope of each genus includes many members with widely differing structural, chemical, and physiochemical properties. Furthermore, each genus is highly variable because a significant number of structural differences between genus members exists.

The specification discloses modified polynucleotides encoding modified Ssp DnaE N-intein and modified Ssp DnaE C-intein and their use in the preparation of modified enzymes including cyclic dihydrofolate reductase and cyclic pseudostellarin F. However, the specification fails to provide a written description of representative members of each claimed genus.

Recitation of the names "inteins", "split inteins", "split inteins derived from RecA, DnaB, PspPol-I, or Pfu inteins", and "split inteins derived from SspDnaE" do not define any specific nucleotide sequence and structure that is common to the members of each claimed genus. Neither the specification nor the general knowledge of those skilled in the art provide evidence of any nucleotide sequence and structure which would be expected to be common to the members of each claimed genus. Thus, one skilled in the art therefore cannot visualize or recognize the identity of the members of each genus.

In view of the above considerations, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of a genus of inteins; a genus of split inteins; a genus of split inteins derived from RecA, DnaB, PspPol-I, or Pfu inteins; a genus of split inteins derived from SspDnaE.

### ***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Holford et al.

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(Structure. 1998 Aug 15;6(8):951-6; PTO 1449 filed 6/15/2001).

Holford et al. teach the concept of how head-to-tail cyclized recombinant peptides and proteins could be made using the taught Expressed Protein Ligation (EPL) and nucleic acids encoding, where introduction of an N-terminal cysteine and a C-terminal thioester within the same polypeptide chain allows for intramolecular native chemical ligation; and that this process has been used to prepare synthetic circular protein domain (see entire document, especially p. 955, penultimate paragraph)

The specification defines the word "intein" is a polypeptide sequence that can catalyze a splicing reaction during post-translational processing of a protein (see p. 13, lines 3-5). Thus, when the teachings Holford et al. are read in view of this definition of "intein", the N-terminal polypeptide sequence of the recombinant protein containing the introduced N-terminal cysteine is deemed to be the first portion of a split intein; the C-terminal polypeptide sequence containing the introduced C-terminal thioester is deemed to be the second portion of a split intein; and the polypeptide sequence in between is deemed to be the target peptide that is to be cyclized.

Thus, the reference teachings anticipate the claimed invention.

### *Claim Rejections - 35 U.S.C. § 103*

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 14-40 and 53-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guan et al. (US Patent 5,643,758) in view of Holford et al. (Structure. 1998 Aug 15;6(8):951-6; PTO 1449 filed 6/15/2001).

Guan et al. teach expression vectors, prokaryotic and eukaryotic host cells, and methods for making, expressing, isolating, and purifying any protein fused to the *E.coli* maltose binding protein (MBP) using the said expression vectors, prokaryotic and eukaryotic host cells; and that these methods and products are useful for purifying virtually any hybrid polypeptide molecule

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employing recombinant techniques (see entire publication of US Patent 5,643,758).


The teachings of Holford et al. have been stated above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Guan et al. such that the nucleic acid molecules taught by Holford et al. are substituted into the vectors, host cells, and method for making polypeptides taught by Guan et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this for the purposes of creating a beneficial method for producing cyclic proteins and enzymes. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

### ***Conclusion***

11. No claim is allowed.
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.
13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

  
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